Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A computer-implemented method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity the same as a biological activity of the reference protein or peptide; which method comprises the steps of:

a) providing a coordinate set representing the backbone of ~~said~~ the 3D structure;

b) constructing a reduced virtual representation for the 3D structure provided in step (a), wherein in ~~said~~ the reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres;

c) determining for each amino acid position along the virtual structure representation provided in step (b) its solvent accessibility;

d) constructing an initial amino acid sequence by assigning for each amino acid position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of ~~said~~ the position;

e) randomly selecting one or more positions along the sequence provided in step (d) and applying on each position a Monte-Carlo simulation in sequence space and rotamer space, ~~said~~ the simulation comprising one or more scoring function calculating steps which include:

i) randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for ~~said~~ the position to obtain a mutation;

ii) for each of the one or more selected positions, calculating an energy difference delta E, between the amino acid residue at the position in the predetermined protein or peptide and each of the one or more selected amino acid residues provided in step (i) based on its ~~said~~ the reduced virtual representation;

iii) selecting a rotamer having a minimal delta E, or when more than one amino acid are manipulated simultaneously, selecting a rotamer combination having a minimal delta E;

iv) accepting the mutation with the rotamer or rotamer combination selected in step (iii) if delta E<0; and

v) assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to ~~said~~ the position(s) and moving to

another position along the sequence;

wherein ~~said~~ the simulation steps are repeated until for each position along ~~said~~ the sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score;

f) expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the structure of the predetermined protein or peptide; and

g) ~~creating~~ outputting a computer output of the expanded all-atom representation of the primary structure(s) obtained in step (f) that predicts at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of the predetermined reference protein or peptide, and wherein the at least one amino acid sequence has a biological activity the same as a biological activity of the reference protein or peptide.

2. (Original) The method as claimed in claim 1, wherein the 3D structure provided in step (a) is that of a native peptide, or protein, or of a designed protein.

3. (Currently amended) The method as claimed in claim 1, wherein ~~said~~ the coordinate set is provided in a computer readable form.

4. (Currently amended) The method as claimed in claim 1, wherein ~~said~~ the amino acid sequence ~~may comprise~~ comprises naturally occurring amino acid residues, synthetic amino acid residues, or variations of ~~said~~ the naturally occurring or synthetic amino acid residues.

5. (Currently amended) The method as claimed in claim 1, wherein for each position along the 3D structure its solvent accessibility is determined according to the extent of exposure of ~~said~~ the position to the solvent surrounding it, ~~said~~ the position being either buried, exposed or intermediate position.

6. (Currently amended) The method as claimed in claim 5, wherein ~~said~~ the solvent is an aqueous solvent.

7. (Currently amended) The method as claimed in claim 6, wherein ~~said~~ the buried positions are occupied by hydrophobic amino acid residues.

8. (Currently amended) The method as claimed in claim 7, wherein ~~said~~ the hydrophobic amino acid residues are each independently selected from the group consisting of Ala, Tyr, Trp, Val, Leu, Ile, Phe, Met, Cys, Pro, and Gly.

9. (Currently amended) The method as claimed in claim 5, wherein ~~said~~ the exposed positions are occupied by hydrophilic amino acid residues.

10. (Currently amended) The method as claimed in claim 9, wherein ~~said~~ the hydrophilic amino acid residues are each independently selected from the group consisting of Lys, Arg, His, Glu, Asp, Gln, Asn, Ser, and Thr.

11. (Currently amended) The method as claimed in claim 5, wherein ~~said~~ the intermediate positions are occupied by either hydrophilic or hydrophobic amino acid residues.

12. (Currently amended) The method as claimed in claim 11, wherein ~~said~~ the intermediate positions are occupied by amino acid residues each being independently selected from the group consisting of Pro, Lys, Arg, His, Glu, Asp, Gln, Asn, Ser, Thr, Gly, Ala, Tyr, Trp, Val, Leu, Ile, Phe, Met, and Cys.

13. (Currently amended) The method as claimed in claim 1, wherein ~~said~~ the Monte Carlo simulation is applied simultaneously on up to three random positions in ~~said~~ the sequence.

14. (Currently amended) The method as claimed in claim 1, wherein ~~said~~ the Monte Carlo step is conducted either at a fixed temperature or at a varying annealing temperature.

15. (Original) The method as claimed in claim 1, wherein a de novo amino acid sequence is generated.

16. (Currently amended) The method as claimed in claim 1, wherein ~~said~~ the amino acid sequence folds under physiological condition into a biologically functional 3D conformation substantially identical to the structure of the predetermined protein or peptide or to a portion thereof.

17. (Previously presented) The method as claimed in claim 15, wherein ~~said~~ the de novo amino acid sequence stabilizes ~~said~~ the 3D structure, as compared to a native amino acid sequence.

18. (Withdrawn) An amino acid sequence which folds under physiological conditions into a specified 3D structure, said amino acid sequence is obtained by the method of claim 1.

19. (Withdrawn) An amino acid sequence according to claim 18, which is biologically functional.

20. (Withdrawn) A nucleic acid sequence encoding the amino acid sequence of claim 18.

21. (Withdrawn) A computer-based system for predicting an amino acid sequence compatible with a predefined 3D structure according to the method of claim 1, said system comprising:

a. input apparatus for specifying said 3D structure;

b. a first memory for storing the specified 3D structure;

c. a second memory having a stored thereon an application program which when running, provides at least one amino acid sequence compatible with the specified 3D structure;

d. a third memory for storing the at least one amino acid sequence obtained;

e. a processor coupled to said input means, and to said first, second and third memories for representation of said amino acid sequence; and optionally, a display unit coupled to said processing means for displaying the amino acid sequence.

22. (Currently amended) The method as claimed in claim 16, wherein ~~said~~ <u>the</u> de novo amino acid sequence stabilizes ~~said~~ <u>the</u> 3D structure, as compared to a native amino acid sequence.

23. (Currently amended) A means for practicing the method of claim 1, comprising:

a computer based system for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide, ~~said~~

the system comprising:

a) input apparatus for specifying ~~said~~ the 3D structure;

b) a first memory for storing the specified 3D structure;

c) a second memory having stored thereon an application program which when running, provides at least one amino acid sequence compatible with the specified 3D structure;

d) a third memory for storing the at least one amino acid sequence obtained;

e) a processor coupled to ~~said~~ the input apparatus ~~means~~, and to ~~said~~ the first, second and third memories for representation of ~~said~~ the amino acid sequence; and

f) optionally, a display unit coupled to ~~said~~ the processor for displaying the amino acid sequence.

24. (Previously presented) The method as claimed in claim 1, wherein the method does not utilize the dead-end elimination algorithm to eliminate rotamers that are mathematically provable to be inconsistent with a global minimum energy solution of a system.

25. (Currently amended) A computer-implemented method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a

biological activity the same as a biological activity of the reference protein or peptide; consisting of:

a) providing a coordinate set representing the backbone of ~~said~~ the 3D structure;

b) constructing a reduced virtual representation for the 3D structure provided in step (a), wherein in ~~said~~ the reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres;

c) determining for each amino acid position along the virtual structure representation provided in step (b) its solvent accessibility;

d) constructing an initial amino acid sequence by assigning for each amino acid position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of ~~said~~ the position;

e) randomly selecting one or more positions along the sequence provided in step (d) and applying on each position a Monte-Carlo simulation in sequence space and rotamer space, ~~said~~ the simulation comprising one or more scoring function calculating steps which include:

i) randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for ~~said~~ the position to obtain a mutation;

ii) for each of the one or more selected positions, calculating an energy difference delta E, between the amino acid residue at the position in the predetermined protein or peptide and each of the one or more selected amino acid residues provided in step (i) based on its ~~said~~ the reduced virtual representation;

iii) selecting a rotamer having a minimal delta E, or when more than one amino acid are manipulated simultaneously, selecting a rotamer combination having a minimal delta E;

iv) accepting the mutation with the rotamer or rotamer combination selected in step (iii) if delta E<0; and

v) assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to ~~said~~ the position(s) and moving to another position along the sequence;

wherein ~~said~~ the simulation steps are repeated until for each position along ~~said~~ the sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score;

f) expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom

sequence representation thereby obtaining an amino acid sequence compatible with the structure of the predetermined protein or peptide; and

g) creating a computer output of the expanded all-atom representation of the primary structure(s) obtained in step (f).